REMARKS

In an Office Action dated December 6, 2007, claims 1-6, 9, 11, 14-17, all of the claims then under consideration in the above-referenced U.S. patent application, were rejected. Applicants respectfully request reconsideration and withdrawal of the outstanding Office Action rejections based on the foregoing amendments and following remarks.

Independent claim 1 has been amended to put the application in better condition for allowance. The subject matter of claim 3 has been incorporated into claim 1 to better define the invention and claims 2 and 3 have been canceled. Claim 15 has been recast in independent form as suggested by the Examiner on page 5, last line of the Office Action. New claim 19, depending from claim 1 has been added to further describe the effective concentration range of the invention. Support for this claim can be found in paragraph [0023] of the specification. New dependent claims 20 and 21 have been added to further describe the effective dosage range of the invention. Support for this claim can be found in paragraph [0014] of the specification. No new matter is added.

Claims 1-6, 9, 11, 14-17 were rejected under 35 U.S.C. §112, first paragraph, on grounds of lack of enablement. This rejection is respectfully traversed.

In the Office Action, it is stated that selecting compounds at random, and attributing randomly selected properties to them, tends to produce unpredictable results.

First of all, the rejected claims are not directed to random compounds and randomly attributed properties. The claims relate specifically to actin-binding and actin-sequestering peptides which contain an actin binding motif, including amino acid sequence LKKTET and conservative variants thereof. The term "conservative variant" is defined in the specification as denoting "the replacement of an amino acid residue by another, biologically similar residue". Examples of conservative variations include the replacement of a hydrophobic residue such as isoleucine, valine, leucine or methionine for another, the replacement of a polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. A description of the physiological activities of the presently claimed compositions which result in the radiation damage-inhibiting effects of the present invention are described in paragraphs [0009-0013] of the specification.

Furthermore, LKKTET and conservative variants thereof, as defined above, include an actin-binding region, active variations of which are found in other actin-binding proteins including those set forth in the paragraph [0018] of the specification, e.g., vitamin D binding protein (DBP) (LKERLQ), cofilin (LKSKMI), depactin (LKMKYS), villin (LKKEKG), and beta-actinin (LKHIES). Polypeptides having such motifs are known in the art to have actin-binding or actin-sequestering activity.

As further evidence that the written description would enable one skilled in the art to practice the presently claimed invention, Applicants are submitting herewith references demonstrating that persons skilled in the art would recognize that other actin-binding or actin-sequestering polypeptides besides thymosin β4 (TB4) can achieve the object of the present invention. The present specification identifies LKKTET as a sequence which is being able to bind to or sequester actin. The specification further points out that actin-binding or actin-sequestering peptides such as peptides containing amino acid sequence LKKTET or conservative variants thereof have activity corresponding to TB4. There is no evidence of record that sheds any doubt on Applicant's disclosure. To the contrary, submitted herewith are a number of references demonstrating corresponding activity of polypeptides containing LKKTET or conservative variants thereof. For example, Rho et al. (2004) identifies the LKKTET sequence as being active in actin binding and sequestration, and as having an important role in maintaining cellular functions, such as cell morphology, proliferation and locomotion (see, e.g., paragraph bridging columns 1 and 2 of the attached Rho et al. publication). Also, Vancompernolle et al. (1991) identifies many conservative variants of LKKTET that have actin-binding or actin-sequestering activity including actobindin (LKHAET), tropomyosin (LKEAET), actinin (LKHIES), plastin (LKRAES), fimbrin (LRRAEC), and myosin (LKSAET).

Other references submitted herewith that show the corresponding activity of LKKTET peptides, conservative variants thereof, and other actin-binding or actin-sequestering peptides, include Wyczólkowska et al. (2007), Irobi et al. (2004), Vaduva et al. (1997), Paunola et al. (2002), Hertzog et al. (2004), Vermeulen et al. (2004), Herrmann et al. (2005),

Van Troys et al. (1996), Eadie et al. (2000) Hannappel (2007), Huff et al. (2001) and Philp et al. (2003).

Applicants submit that the amended claims no longer recite the treatment or prevention of damage due to radiation, nor do they specify actin-sequestering agents or anti-inflammatory agents. Furthermore, the claims have been amended to identify only specific radiation damage-inhibiting polypeptides. These specific polypeptides have actin-binding or actin-sequestering activity. The claims have also been further limited to recite an effective concentration range of about 0.005 - 0.1% by weight. Support for this range can be found in paragraph [0023] of the specification. Thus, the present claims relate only to a specific concentration range of specific actin-binding or actin-sequestering compounds with radiation damage-inhibiting activity. The references submitted herewith support the disclosure in the specification of the corresponding activities of polypeptides containing LKKTET and conservatives variants thereof. Thus, Applicants submit that one of ordinary skill in the art would be enabled to practice the presently claimed invention.

Claims 1 and 15 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner asserted that the skilled medical practitioner would not know who the subject is in need of "such treatment". Claim 1 has been amended to relate to a method of inhibiting radiation damage by first administering (the compound) to a subject and then administering radiation to a target area of said subject. Thus, the skilled medical practitioner would know exactly who the subject in need of such treatment would be since said subject would be scheduled to undergo radiation treatment. Claim 15 has been rewritten in independent form as suggested by the Examiner.

Claim 1 was rejected under 35 U.S.C. §103 as obvious in view of Rudolph (US 200601668877). The Examiner states that "Rudolph discloses the use of thymosin for treating or preventing radiation damage". Applicants respectfully traverse this rejection.

Rudolph only discloses administration of an alpha thymosin peptide. The amino acid sequence of thymosin alpha 1 is SDAAVDTSSEITTKDLKEKKEVVEEAEN. Thymosin alpha 1 and thymosin beta 4 both originally were derived from the thymus gland. However, thymosin beta 4 later was found to be a ubiquitous molecule present in all human cells, and is actin-binding, which thymosin alpha 1 is not. Thus, thymosin β4 was originally

characterized as a thymic protein because of the accidental way that it was first discovered. As shown in the attached OMIM entry number 300159, third full paragraph, although thymosin β4 was originally isolated from a partially purified extract of calf thymus, thymosin β4 is ubiquitous in that it has been found in the body in all tissues and cell lines analyzed.

The present claims specify amino acid sequence LKKTET, a conservative variant of LKKTET (as defined in paragraph [0019] of the specification), KLKKTET, LKKTETQ, an N-terminal variant of Tβ4, a C-terminal variant of Tβ4, an isoform of Tβ4, a splice-variant of Tβ4, oxidized Tβ4, Tβ4 sulfoxide, lymphoid Tβ4, pegylated Tβ4, $T\beta4^{ala}$, Tβ9, Tβ10, Tβ11, Tβ12, Tβ13, Tβ14, Tβ15, gelsolin, vitamin D binding protein (DBP), profilin, cofilin, adsevertin, propomyosin, fincilin, depactin, Dnasel, vilin, fragmin, severin, capping protein, β-actinin or acumentin.

Claim 1 was rejected under 35 U.S.C. §103 as obvious in view of Greenberger (US 5,599,712). Greenberger discloses a method protecting a subject against an agent that elicits production of toxic free radicals, superoxide anions, or heavy metal cations in the subject consisting of the in vivo administration to the subject a polynucleotide encoding a protein that is transiently expressed in said subject. An object of the invention is to provide intracellular therapeutic quantities of metallothionein, superoxide dismutase or gamma glutamyl transpeptidase in normal tissues in vivo adequate to furnish protection against ionizing radiation or an anticancer agent. The proteins of the invention that are capable of neutralizing or elimination the toxic species can be gamma glutamyl transpeptidase, manganese superoxide dismutase, or metallothionein (abstract, col.2 lines 17-21, 28-43).

According to the Office Action, one or more of the proteins could qualify as an "anti inflammatory" agent within the meaning of instant claim 1. Claim 1 has been amended to delete "an anti-inflammatory agent". Greenberger does not disclose or make obvious a radiation damage-inhibiting polypeptide comprising amino acid sequence LKKTET, a conservative variant of LKKTET, KLKKTET or LKKTETQ. Furthermore, Greenberger does not disclose or make obvious an N-terminal variant of Tβ4, a C-terminal variant of Tβ4, an isoform of Tβ4, a splice-variant of Tβ4, oxidized Tβ4, Tβ4 sulfoxide, lymphoid Tβ4, pegylated Tβ4, $T\beta4^{ala}$, Tβ9, Tβ10, Tβ11, Tβ12, Tβ13, Tβ14, Tβ15, gelsolin, vitamin D binding protein (DBP), profilin, cofilin, adsevertin, propomyosin, fincilin, depactin, Dnasel, vilin, fragmin,

severin, capping protein, β-actinin or acumentin. Thus, Greenberger does not disclose or render the subject matter of the present claims obvious.

Claim 1 was rejected under 35 U.S.C. §103 as obvious in view of Barcellos-Hoff (US 5,616,561). Barcellos-Hoff discloses mitigation of radiation induced tissue damage by administering a Transforming Growth Factor β antagonist. Claim 1 has been amended to delete "an antagonist of said compound" and "an agent which regulates said compound". Thus, the disclosure of Barcellos-Hoff does not render the present claims obvious.

Claim 1 was rejected under 35 U.S.C. §103 as obvious in view of Rogers (US 7,173,011). Rogers discloses methods and kits for mitigating radiation therapy, to support bone marrow transplantation, and promoting megakaryocyte production and mobilization and platelet production, each method comprising the administration of an effective amount of angiotensinogen, angiotensin I(AI), AI analogues, AI fragments and analogues thereof, angiotensis II(AII), AII analogues, AII fragments or analogues thereof or AII AT2 type 2 receptor agonists (abstract). The Office Action asserts that one or more of the compounds disclosed would fall within the scope of the instant claim 1 and thus claim 1 is rendered obvious. Rogers relates to a polypeptide with amino acid sequence D-R-V/P-Y-I/A-H-P-I. The present claims do not relate to any of the compounds or amino acid sequences disclosed in Rogers. Rogers does not disclose a radiation damage-inhibiting polypeptide comprising amino acid sequence LKKTET, a conservative variant of LKKTET, KLKKTET, LKKTETQ, an N-terminal variant of Tβ4, a C-terminal variant of Tβ4, an isoform of Tβ4, a splice-variant of Tβ4, oxidized Tβ4, Tβ4 sulfoxide, lymphoid Tβ4, pegylated Tβ4, $T\beta4^{ala}$, Tβ9, Tβ10, Tβ11, Tβ12, Tβ13, Tβ14, Tβ15, gelsolin, vitamin D binding protein (DBP), profilin, cofilin, adsevertin, propomyosin, fincilin, depactin, Dnasel, vilin, fragmin, severin, capping protein, β-actinin or acumentin. Thus, the disclosure of Rogers does not render the present claims obvious.

Claims 1-6, 9, 11, 14-17 were rejected under 35 U.S.C. §103 as obvious in view of Kleinman (US 2007/0111931). Kleinman discloses that thymosin beta 4 is "useful for repair of tissue resulting from injuries due to surgical procedures, irradiation, laceration, toxic chemicals, viral infections, bacterial infections, or burns" (paragraph [0046]). The present claims have been amended to specify a method of inhibiting radiation damage to tissue of a subject by first administering a radiation damage-inhibiting, actin-binding or actin-

sequestering polypeptide comprising amino acid sequence LKKTET, a conservative variant of LKKTET, KLKKTET, LKKTETQ, an N-terminal variant of Tβ4, a C-terminal variant of Tβ4, an isoform of Tβ4, a splice-variant of Tβ4, oxidized Tβ4, Tβ4 sulfoxide, lymphoid Tβ4, pegylated Tβ4, $T\beta4^{ala}$, Tβ9, Tβ10, Tβ11, Tβ12, Tβ13, Tβ14, Tβ15, gelsolin, vitamin D binding protein (DBP), profilin, cofilin, adsevertin, propomyosin, fincilin, depactin, Dnasel, vilin, fragmin, severin, capping protein, β-actinin or acumentin, the composition comprising said compound at a concentration of about 0.005 - 0.1% by weight, then administering radiation to a target area of said subject, thereby inhibiting radiation damage in said subject.

Accordingly, all rejections have been fully addressed and it is believed that independent claims 1 and 15 are now allowable over the cited references. Claims 4-6, 9, 11, 14, and 19-21 depending from claim 1, and claims 16 and 17, depending from claim 15, are also allowable, at least for the reasons discussed above. Withdrawal of all of the rejections is respectfully requested.

An initial sequence listing is attached to this paper and its entry into the application is respectfully requested. The specification has been amended to insert sequence identifier numbering. No new matter is introduced by means of these amendments.

In view of the foregoing amendment and remarks presented herein, Applicants respectfully submit that this application is in condition for allowance and should now be passed to issue.

A Notice of Allowance is respectfully solicited.

If any extension of time is required in connection with the filing of this paper and has not been requested separately, such extension is hereby requested.

The Commissioner is hereby authorized to charge any fees and to credit any overpayments that may be required by this paper under 37 C.F.R. §§ 1.16 and 1.17 to Deposit Account No. 02-2135.

Respectfully submitted,

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